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Guideline-Directed Heart Failure Therapy in Patients after Left Ventricular Assist Device Implantation: A Review

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Abstract

Background: Left ventricular assist devices (LVADs) are used as an advanced therapy option for patients with stage D heart failure. These devices provide mechanical unloading of the heart as either a bridge to transplant or recovery, or as destination therapy. In patients with LVADs, there are emerging data on the use of heart failure guideline-directed medical therapy (GDMT) to improve outcomes. This review describes the current evidence available for the use of neurohormonal blocking agents in patients with LVADs.
Methods: Articles were found using PubMed and web searches for heart failure therapies/neurohormonal blockade and LVADs. Studies were included if they evaluated the use of the heart failure therapies, either retrospectively or prospectively.
Results: A total of 17 articles and 9 abstracts were reviewed. The totality of data surrounding the use of GDMT neurohormonal blockade in patients with LVADs are limited in nature. Much of the data are limited either by use of surrogate outcomes, single center evaluations, and/or small sample sizes. However, the evidence does support clinical benefit with associated mechanistic plausibility. More research is needed to understand appropriate patient selection and means to optimize these therapies in the LVAD population.
Conclusion: Combined neurohormonal blockade appears to reduce morbidity and mortality in patients with LVAD implants.

Background

The use of mechanical circulatory support with a left ventricular assist device (LVAD) has increased as a treatment option for patients with stage D heart failure (HF).[1] A limited donor pool for orthotopic heart transplantation (OHTx) in conjunction with advancements in LVAD technology have fueled this growth. The available LVADs in the United States have two Food and Drug Administration approved indications for implantation: 1) bridge to transplantation for patients who are candidates for OHTx and at risk of death from stage D HF; or 2) destination therapy for patients who are not candidates for OHTx.[2] A review of the devices' approval history and mechanics are beyond the scope of this article.

According to the 2017 American College of Cardiology /American Heart Association HF guideline updates, LVAD implantation is indicated for eligible patients who have stage D HF with reduced ejection fraction (EF) (HFrEF).[3] Despite these recommendations, there are inherit risks associated with placement of an LVAD due to the invasive nature of the procedure and device; thus, patient selection requires a multidisciplinary approach. After placement of the LVAD, the patient must have extensive education on what activities are permissible and how to manage the device. Management considerations for the LVAD patient include addition of anti-thrombotic therapy, driveline maintenance, and alarm-awareness. However, what is less defined is the role and use of guideline-directed medical therapy (GDMT) for HF. Limited data are available to guide the use of HF therapy following implantation, and the 2020 International Society of Heart and Lung Transplant (ISHLT) mechanical circulatory support (MCS) guidelines only briefly outline recommendations based on these data.[1] Therefore, the purpose of this review is to evaluate the evidence for use of HF GDMT in patients with a durable LVAD. Additionally, we aim to provide treatment recommendations for optimizing GDMT in this patient population.

Methods

Medline and Google Scholar were searched from January 2000 to February 2021 using the term "ventricular assist device" or "LVAD" with each of the following terms: "neurohormonal blockade," "heart failure therapy," "guideline-directed medical therapy," "beta blocker," "beta blockade," "angiotensin converting enzyme," "angiotensin receptor blockers," "ACE," "ARB," "RAAS," "sacubitril-valsartan," "ARNi," "mineralocorticoid receptor antagonist," "aldosterone antagonist," and "MRA." Retrospective and prospective studies were included in abstract and full article format. Studies with animal subjects, written in a language other than English, or with only in vitro or ex vivo data were excluded, as were studies with temporary mechanical circulatory support. Additionally, in the instance that studies were in both published abstract and article format, only the article was included.

Results

Guideline-Directed Medical Therapies

The mechanism behind the combined use of device support and medication is to unload the left ventricle (LV) mechanically and via neurohormonal pathways, such as the renin-angiotensin-aldosterone system (RAAS), to help with myocardial recovery.[4] In this review article, neurohormonal blockade (NHB) was considered to be one or more of the following medication classes which are listed as class I level of evidence A recommendations for chronic HFrEF: angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), angiotensin receptor-neprilysin inhibitor (ARNi), beta blocker (BB), and mineralocorticoid receptor antagonist (MRA).[3]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

In patients with LVADs, the device supports the damaged heart by mechanically unloading the ventricular volume; however, the force of the unloading can contribute to myocardial stiffness. Three articles and one published abstract evaluating the myocardial response to ACEi and ARB therapy in LVAD patients are included in this review.[5-8]

Klotz et al. have investigated the use of ACEi therapy to reduce this sequela in patients supported with HeartMate VE LVADs (Abbott, Chicago, IL).[5,6] In the authors' first study, heart samples were collected during implantation and post-explantation of the LVAD in 22 patients. The 7 subjects in the ACEi group received enalapril, captopril, or lisinopril at approximately 30 days post-implantation until the device was explanted for transplant. In all patients, angiotensin I and II concentrations were higher pre- versus post-LVAD implantation ($p<0.05$). However, at explantation, angiotensin II content was significantly lower in patients receiving ACEi therapy compared to those not on ACEi (81 fmol/g ±7 vs. 262 fmol/g ±41, $p <0.05$). Additionally, the collagen content, LV mass, and myocardial stiffness were significantly decreased with ACEi use ($p<0.05$). These findings suggest reverse remodeling does occur in patients on ACEi therapy after LVAD implantation.[5] Based on the aforementioned results, the authors sought to investigate the effects of ACEi therapy on renin, aldosterone, and norepinephrine in 20 HeartMate VE LVAD patients. At implantation, patients in both groups had renin levels that were 100-fold higher than normal, and resultant cardiac angiotensinogen was diminished. In those not prescribed ACEi post-implant, cardiac aldosterone and renin decreased ($p<0.006$ and $p<0.001$, respectively); whereas, norepinephrine increased by approximately seven-fold ($p=0.004$). ACEi patients did not experience these effects; their aldosterone and renin remained elevated, and norepinephrine did not increase. Thus, ACEi therapy helps to prevent the activation of the sympathetic nervous system in these patients and prevent cardiac fibrosis.[6]

These studies demonstrated a biochemical basis to warrant further evaluation of the clinical effects of neurohormonal modulation in patients with an LVAD (Figure

1). Their small sample sizes, the use of laboratory parameters instead of clinical outcomes, and the low proportion (20%) of female patients, limit the applicability of both of these studies. Additionally, the HeartMate VE is a first generation, pulsatile LVAD that is now obsolete. Thus, comparisions are not applicable to to HeartMate 3 devices and HVADs, which are third generation devices with continuous centrifugal flow and electromagnetic technology.[7]

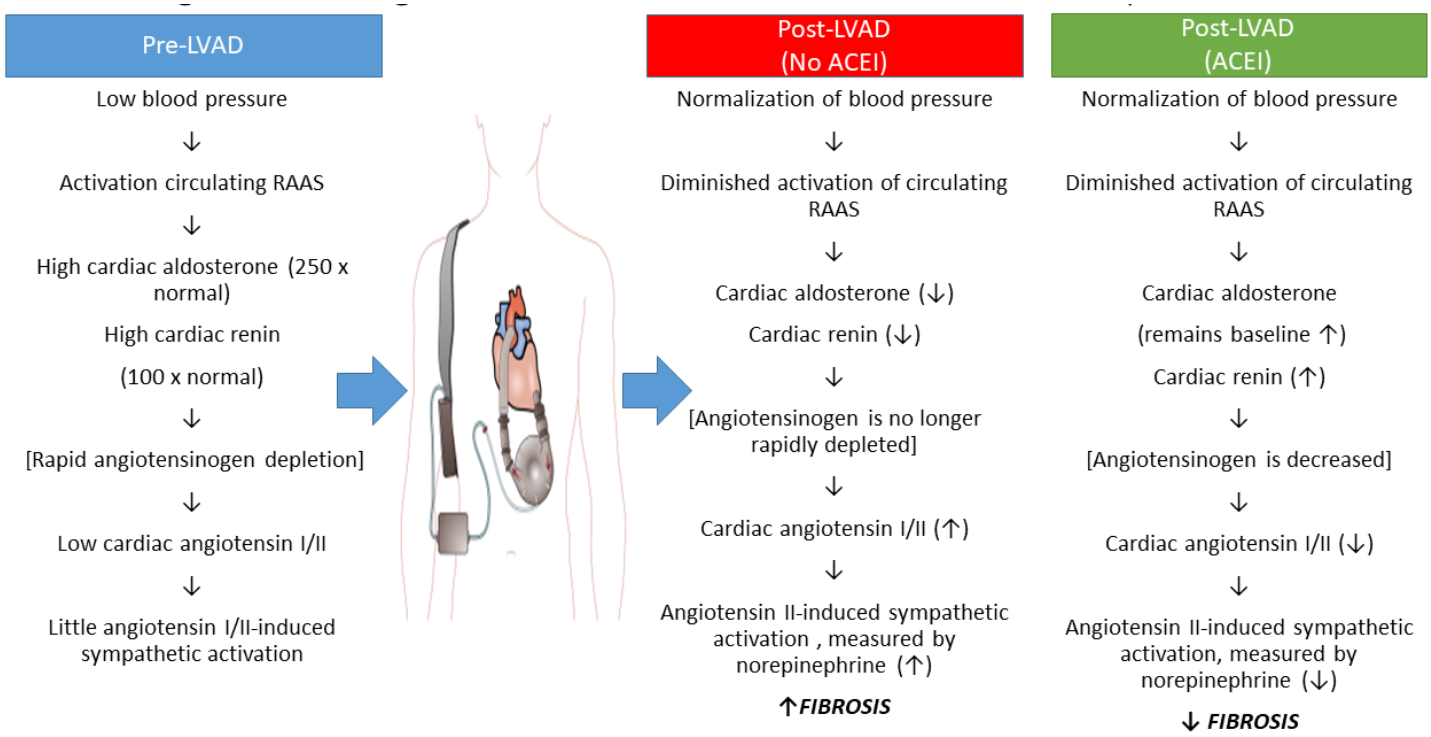

Figure 1. *Changes in the cardiac renin-angiotensin-aldosterone system (RAAS) with and without angiotensin-converting enzyme inhibitor after the implantation of a left ventricular assist device (LVAD).*

In a retrospective study of 307 patients with either a HeartMate II™ (HMII, Abbott, Chicago, IL) or a HeartWare™ ventricular assist device (HVAD, Medtronic, Dublin Ireland), the use of NHB therapy and its impact on mortality was evaluated.[8] Of the patients included, 76.5% were male and 63.5% were Caucasian, with a mean age of 60 years. At 12 months, 30.9% of patients who were alive with an implant were on ACEi or ARB therapy alone or combined with other therapy. ACEi/ARB therapy was associated with decreased mortality when death secondary to neurological conditions, HF, and respiratory failure was analyzed together (HR 0.38 [0.16-0.94], p=0.037). The use of ACEi or ARB therapy in the time-dependent evaluation of mortality post-implant was associated with a 50% decrease in mortality (HR 0.50 [0.29-0.86], p=0.01). Significant differences in patients in the ACEi/ARB group compared to the no-ACEi/ARB group included more African-American patients (33.3% vs. 17.3%, p<0.01), younger patients (57 years vs. 61 years, p<0.01), and

more non-ischemic patients (50.8% vs. 36.4%, p=0.03). Although limited by its retrospective nature, this larger study of more than 300 patients suggests a potential mortality benefit of continued ACEi or ARB use after implantation of an LVAD.

Reduction in mortality was further explored in a retrospective analysis of the ISHLT Mechanically Assisted Circulatory Support (IMACS) registry, including 11,494 patients who were implanted with a continuous-flow LVAD (CF-LVAD) and were alive at 3 months post-implant.[9] Of the patients included, the 50% who were prescribed an ACEi/ARB were compared to propensity score-matched patients without any RAAS blockade. The Cox proportional hazards survival analysis used ACEi as an independent variable and demonstrated an association with survival (HR 0.79 [0.69-0.90], p<0.001). The authors concluded that in patients who tolerate the addition of an ACEi or ARB to their medication regimen, a mortality benefit might be incurred at 12 months after LVAD implantation. This study confirmed the findings of the previous studies in a large outcome and population-based manner. However, given the data are from a registry, it is limited by lack of treatment information, inability to account for confounders, as well as potential under-reporting of the outcomes.

An additional benefit of angiotensin II inhibition is a reduced risk for the development of gastrointestinal bleeding (GIB) secondary to arteriovenous malformations (AVM)—a common complication after LVAD implantation. Four articles addressing the gastrointestinal protective effects of angiotensin II inhibition were included in this review.[10-13] A retrospective analysis was completed that compared 100 patients with either a HMII or HVAD on ACEi or ARB therapy to 31 patients that did not receive either medication. Twenty four percent of the patients in the ACEi/ARB group reported GIB as compared to 48% in the no ACEi/ARB group (OR 0.29, [0.29-0.72]).[10] The results were further delineated into patients experiencing GIB secondary to AVM. Once again, the ACEi/ARB group had a lower incidence (9%) when compared to the no-ACEi/ARB group (29%, OR 0.23 [0.07-0.71]). Because this study was conducted at a single center and was limited by its retrospective nature, it is mostly hypothesis generating.

Similar results were reported in a study of 111 CF-LVAD patients when an ACEi or ARB was initiated within 30 days post-implantation.[11] The patients on ACEi or ARB therapy experienced a 57% reduction in overall GIB rates (HR 0.43, [0.19-0.97], p=0.042) and a 63% reduction in AVM-related GIB (HR 0.37, [0.16-0.84], p=0.017). The authors found the reduction in GIB was most likely to be dose-related with a minimum threshold of an ACEi equivalent of 5 mg of lisinopril daily. The authors did not elaborate in this single center study on other factors that can affect GIB, including other medication therapy that could perpetuate or protect against GIB.

A retrospective analysis of 377 patients with HVAD or HMII LVADs categorized patients according to the number of GIB experienced per year (no bleed, 1 bleed, 1-3 bleeds, >3 bleeds).[12] Results demonstrated that patients with more GIB were less likely to be on an ACEi or ARB compared to patients with no GIB (51% v 79%, p<0.0001). When adjusted for age, sex, Interagency Registry for Mechanically

Assisted Circulatory Support (INTERMACS) profile, bridge-to-transplant status, creatinine, and body mass index, ACEi/ARB therapy was associated with a 67% reduction in the incidence of GIB (95% CI 0.15-0.71, p=0.005).

A meta-analysis of the previous three studies[10-12] determined the relationship between angiotensin II antagonism and GIB in LVADs.[13] The pooled analysis of the CF-LVAD patients (n=619) revealed a significant reduction in GIB in patients receiving ACEi/ARB therapy (OR 0.35, 95% CI 0.22-0.56, I^2=0%, p<0.001). However, there was not a significant reduction in AVM-related GIB (OR 0.46, 95% CI 0.19-0.17, I^2=51%, p=0.07). No publication bias assessment was able to be performed due to the small number of studies included.

The results from these single-center studies suggest ACEi/ARB therapy proves a gastro-protective effect in LVAD patients in addition to the proposed mortality benefit.

Angiotensin Receptor-Neprilysin Inhibitor

Evidence for the use of sacubitril-valsartan in LVAD recipients is limited to date; our literature review found only four published abstracts and one article.[14-18]

In a study of 10 patients who were initiated on sacubitril-valsartan, 6 patients were able to tolerate the maximum dose of 97-103 mg.[14] The results revealed that ARNi therapy was safe, with potassium (mEq/L) and creatinine (mg/dl) differences at baseline and 3 months of 4.2 ±0.3 versus 4.4 ±0.3 and 0.84 ±0.2 versus 0.85 ±0.19, respectively.

In a separate study, 12 HMII patients on sacubitril-valsartan therapy were compared to 12 patients on other anti-hypertensive therapy.[15] Those on sacubitril-valsartan therapy had an average mean arterial pressure (MAP) reduction of 20 mmHg compared to a 12 mmHg reduction in patients on standard anti-hypertensives. Additionally, the authors found a decreased rate of stroke and re-admissions compared to standard of care without an increase in adverse effects, although no numerical details were provided to show the extent of these outcomes.

A single-center, retrospective case series of 10 patients prescribed ARNi therapy post-implant reported a significant reduction in MAP (20.0 ± 14.0 mmHg, p=0.002) and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) (2,929 pg/mL to 1,530 pg/mL, p=0.36).[16] This positive effect was not accompanied by either an increase in serum creatinine or potassium in most patients, with only one report of hyperkalemia that required discontinuation of sacubitril-valsartan.

Similar changes were reported at a center in which 30 LVAD patients prescribed sacubitril-valsartan experienced a significant decrease in NT-proBNP at 6 months (1,082 pg/mL to 651 pg/mL, p=0.013).[17] At 6 months 41% of patients were prescribed 24/26 mg, 27% at 49/51 mg, and 32% at 97/103 mg. These data support the safe and effective use of sacubitril-valsartan as an anti-hypertensive medication, but do not elaborate on heart failure morbidity or mortality outcomes.

A single center evaluated 20 LVAD patients pre- and post-ARNi initiation to determine effects on MAP and HF morbidity.[18] At 3 months post-initiation, MAPs decreased from 92 ±24 to 75 ±19 mmHg (p<0.001), and the New York Heart Association Functional Class improved significantly from 2.6 ±0.8 to 1.6 ±0.7 (p<0.001). Additionally, the authors found a reduction in calcium channel blocker and diuretic dose. Six patients did not tolerate the sacubitril-valsartan and therapy was discontinued.

Initial data for sacubitril-valsartan suggest a physiological and clinical benefit with minimal patients experiencing adverse effects. It is important to note that the patients on ARNi therapy in these studies were stable at baseline. In addition, the small number of patients included, the single center nature, and the lack of baseline demographic information provided in the abstracts limit the ability to apply these data to other patients with LVADs.

Beta Blockers

Despite the accumulating experience with NHB as a therapeutic intervention to improve outcomes for patients with LVADs, the evidence for BB therapy alone is limited to 1 article and 3 published abstracts.[19-22]

A retrospective study from Japan examined factors predictive of LV reverse remodeling (LVRR) in 60 patients with non-ischemic dilated cardiomyopathy who received either pulsatile or CF-LVAD support as a bridge to recovery.[19] Patients were treated pre-operatively with standard medical therapy that consisted of BB (carvedilol or bisoprolol), ACEi, ARBs, and MRA as tolerated. The endpoint of LVRR was defined as a left ventricular ejection fraction (LVEF) of ≥35% at 6 months post-LVAD or explantation of LVAD within 6 months. Overall, 27% of the study cohort achieved LVRR, and 10% were explanted. The authors found that lower titrations of pre-operative BB use and pulsatile flow LVADs were each significantly associated with LVRR during LVAD support. Furthermore, a dose-dependent relationship with BB treatment was apparent on univariate analysis (maximum dose of BB, 2.7 ± 3.5 vs. 9.9 ± 6.4 mg/day in carvedilol equivalents [5 mg bisoprolol equivalent to 20 mg carvedilol]; p=0.015). The authors used multivariate analysis to identify a threshold of a cumulative BB dose of <1.6 gm (p=0.005). The authors concluded that the impact of post-operative BB use is most effective in patients who were not maximized on BB therapy pre-operatively. Doses of BB were well described in this study, although the information provided regarding pulsatile flow LVADs has limited applicability in the current era of CF devices.

Other retrospective studies of BB use in the LVAD population have been reported in abstract form.[20-21]

A review of 98 patients with CF-LVAD showed that BB use (n=72) compared to non-use (n=26) was associated with lower NT-proBNP concentrations at 6 and 12 months post-LVAD implant without an increase in hospitalizations.[20] There was a trend toward fewer deaths in the BB group (6% vs. 15%). Notably, approximately half the patients in this study had greater than moderate right ventricular dysfunction.

Another study of CF-LVAD patients evaluated differences in outcomes between carvedilol and metoprolol. Among 220 patients, 85% received a BB at the time of the first outpatient visit.[21] The authors reported a lower risk for pump thrombosis with carvedilol (p = 0.04), despite a trend toward more GIB as compared to metoprolol (p=0.08).

Finally, a study of 159 patients demonstrated that BB use compared to non-use was independently associated with survival in patients with a CF-LVAD (HR 0.33, 95% CI 0.15-0.71; p = 0.006).[22]

Limitations of each of these studies include the retrospective design and relatively small patient cohorts. Decisions about BB use, agent selection, and dose were left to prescriber discretion in each study. Nonetheless, signals of improved outcome with BB use for the CF-LVAD patient population were evident and support modern registry data, which illustrates a beneficial role for NHB in these patients.[1] The available data indicate the use of one of the three BBs with an indication in chronic HF at maximally tolerated doses leads to ventricular recovery and improved survival. Optimal dosing and effects on right ventricular activity still need to be elucidated with further research.

Mineralocorticoid Receptor Antagonists

To date, two abstracts have been published evaluating MRA use in patients with LVADs. However, the results of abstracts indicate conflicting results with regards to cardiac recovery. In a one abstract of 27 patients, the 14 patients who were prescribed MRAs had a greater improvement in LVEF compared to those who were not (18 ±2 to 37 ±4 vs. 20 ±3 to 27 ±4%, p<0.01).[23] In the MRA group, 93% were prescribed BB and 85% received an ACEi in comparison to 100% and 62% in the non-MRA group. This study is a post-hoc analysis of a prospective study at a single center, limiting the interpretation of the statistical analysis.

Brinkley et al. included 2,670 patients prescribed MRAs in their analysis of RAAS-modulating medications.[9] Similar to the ACEi/ARB arm, survival was improved in the MRA versus no RAAS (p=0.03). However, when results were adjusted for known predictors of survival in the Cox proportional hazards analysis, MRA use was not associated with improved survival (HR 0.94 [95% CI 1.02-1.49], p=0.33). The authors do not include further information on doses received by patients, length of time on therapy, or differences in other therapies between groups.

Combined Neurohormonal Blockade

Eight articles have evaluated the use of combined NHB in patients with durable LVADs and are included in this review.[24-31] The majority of these articles focus on the intent of device explantation.[24-29] In patients who were evaluated for bridge to recovery with optimization of device support and medication regimens, there are inconsistencies in the agents used and the duration of therapy (Table 1).

Table 1. Summary of studies evaluating combined neurohormonal blockade for bridge to recovery

Study	VAD	Criteria for Recovery	Baseline	Medication Regimen Targeted[a]	Mean Doses Achieved	Outcomes
Matsumiya, 2005[24] Retrospective case series	HeartMate-IP™ [b] HeartMate-VE™ [c] Novacor™ [d]	LVEF >45%, LVEDD <55 mm, stable BNP, no deterioration in LV function during LVAD off-test	11 Patients 100% DCM 91% male Age range: 15-38 years (mean 27.9±7.6 years)	ACEi not described Carvedilol 40 mg/day Spironolactone Digoxin	Not described, only 1 patient tolerated beta blockade	• 5 (45%) explanted • Mean duration of support 429.4±156.5 days • 100% survival 2 years
Birks, 2006[25] Prospective cohort study	HeartMate I™ [c]	LVEF >45% LVEDD <60 mm LVESD <50 mm LVEDP <12 mmHg CI >2.8 L/min/m Maximal VO_2 >16 mL/kg/min All maintained with LVAD off for 15 minutes	15 patients 100% NICM 80% male Age range: 15-56 years Duration of HF: 1-156 months	Lisinopril 40 mg/day Losartan 100 mg/day Carvedilol 50 mg BID Spironolactone 25 mg/day Bisoprolol 10 mg/day + clenbuterol 700 mcg TID replaced carvedilol after maximal regression in LVEDD	Not described	• 5 (45%) explanted • Mean duration of support 429.4±156.5 days • 100% survival 2 years
Birks, 2011[26] Prospective cohort study	HeartMate II™	LVEF >45% LVEDD <60 mm LVESD <50 mm LVEDP <12 mmHg CI >2.8 L/min/m Maximal VO_2 >16 mL/kg/min All maintained with LVAD at 6000 RPM for 15 minutes	20 patients 100% NICM 80% male Age range: 16-58 years Duration of HF 1.5-132 months	Lisinopril 40 mg/day Losartan 100 mg/day Carvedilol 25 mg TID Spironolactone 25 mg/day Digoxin 125 mcg/day Bisoprolol 10 mg/day + clenbuterol 700 mcg TID replaced carvedilol after maximal regression in LVEDD	After Phase I: Lisinopril 31.25±13.7 mg Losartan 77.8±26.4 mg Carvedilol 37.2±16.3 mg Spironolactone 25±0 mg Digoxin 121.7±14.3 mcg Bisoprolol 9.4±3.1 mg Clenbuterol 1886.3±459.5 mcg	• 12 (60%) explanted • Mean duration of support 286 ± 97 days • 83.3% survival at 30 days and 3 years

[a]Goal doses listed; [b]Thermo Cardiosystems, Inc, Woburn, MA; [c]Thoratec Corp., Pleasanton, CA; [d]World Heart Corp., Salt Lake City, UT; DCM: dilated cardiomyopathy; NICM: non-ischemic cardiomyopathy; BID: twice daily; TID: three times daily; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVEDP: left ventricular end-diastolic pressure; CI: cardiac index; VO2: oxygen consumption; HF: heart failure; RPM: revolutions per minute

Table 1 Continued. Summary of studies evaluating combined neurohormonal blockade for bridge to recovery

Study	VAD	Criteria for Recovery	Baseline	Medication Regimen Targeted[a]	Mean Doses Achieved	Outcomes
Lamarche, 2011[27] Prospective cohort study	HeartMate II™	LVEF >40% and LVEDD <55 mm Good right ventricular function, and no structural dysfunction	17 patients enrolled, 4 patients explanted 75% NICM & 25% ICM explanted: 50% male Age range: 19-51 years	ACEi or ARB or hydralazine Beta blockers Spironolactone (doses and specific medications not described)	Not described	• 4 (24%) explanted • Mean duration of support 213 days (range 70-293) Recovered vs. non-recovered • Duration of HF 10.2±8 vs. 53.8±36.2 months, p=0.28
Patel, 2013[28] Prospective cohort study	HeartMate II™ VentrAssist™ [e]	LVEF >40%	31 patients enrolled, 21 patients completed testing 38% ICM 62% NICM 76% male Age range: 22-72 years Duration of HF 10-3,600 days	Lisinopril 40 mg/day OR Losartan 100 mg/day OR Hydralazine/isosorbide dinitrate 225/120 mg Carvedilol 50 mg BID OR Metoprolol succinate 200 mg/day Spironolactone 25 mg/day	Lisinopril 17.9±13.2 mg Hydralazine: 180.5±69 mg Nitrates: 77.1±35.2 mg Carvedilol: 49.6±21.9 mg Spironolactone 31.9±13.5 mg	• 5 (24%) patients with recovered function, 3 (14%) explanted • Mean duration of support 289±117 days • 100% survival of explants at 3 years Recovered subjects vs. non-recovered • Body surface area: 1.9±0.2 vs. 2.1±0.2 m2, p=0.075 • Duration of HF: 79±81 vs. 1,053±1,187 days, p=0.005 • LVAD speed: 9,240±219 vs. 8,946±277 rpm, p=0.037
Birks, 2020[29] Prospective cohort study	HeartMate II™	LVEF >45% LVEDD <60 mm LVESD <50 mm LVEDP <15 mmHg CI >2.4 L/min/m Maximal VO_2 >16 mL/kg/min All maintained with LVAD at 6000 RPM for 15 minutes	36 patients 100% NICM 67.5% male Mean age 35.1±10.8 years Duration of HF 20.8±20.6 months	Lisinopril 20 mg BID Losartan 150 mg/day Carvedilol 50 mg BID Spironolactone 25 mg/day Digoxin 125 mcg/day	Not described	• 19 (73%) explanted • Mean duration of support 1.06±0.59 years • 78.9% remain explanted, free of transplantation

[e] *Ventracor Ltd, Brisbane, QLD, Australia*

The most well-defined medication regimens were described by Birks et al. in patients with HeartMate I™ (Abbott, Chicago, IL), and later, HMII devices.[25,26,29] These subjects prospectively underwent two stages of medication therapy in the Harefield Protocol.[25,26] The patients included in these studies all had non-ischemic cardiomyopathy supported with HeartMate™ devices and tended to be younger males with a shorter duration of HF prior to LVAD. The first stage of the Harefield Protocol for medication titration is well-described and indicates aggressive up-titration of NHB early post-implant can be safe and leads to improvement in cardiac parameters. Stage one consisted of initiation of lisinopril, carvedilol, spironolactone, and losartan. After inotropic wean post-implant, these four medications were up-titrated to maximally tolerated doses. Stage two started after patients maintained the maximal regression in LV end diastolic diameter (LVEDD) for two weeks. At this point, patients were converted from carvedilol therapy to bisoprolol, and clenbuterol (a beta2 adrenergic agonist) was added at 40 mcg twice daily and titrated to a dose of 700 mcg three times daily. Explantation was performed in patients who maintained LVEF >45% and LVEDD <60 mm, along with other cardiac parameters (Table 1). With this protocol the explant rate was 73% in HeartMate I devices with a mean duration of support of 320 ± 186 days, and 60% in HMII devices with a mean duration of support of 286 ±97 days.[25,26]

In the largest study conducted by Birks et al. with 36 HMII patients, 19 total patients had their LVAD removed under the study protocol.[29] The following medications were initiated after inotropes were weaned off: lisinopril (goal 20 mg twice daily); carvedilol (goal 50 mg twice daily); spironolactone (goal 25 mg daily); digoxin (goal 125 mcg daily); and losartan (150 mg daily). Medications were titrated to achieve a MAP >60 mmHg with no upper limit. Phase two of the previously mentioned Harefield Protocol was not used in this study. Sixteen (44%) of patients met the primary endpoint of explant within 18 months with freedom from mechanical circulatory support and heart transplantation at one year after explant ($p<0.01$). Lower preoperative serum creatinine was associated with a higher chance of recovery in univariate analysis ($p<0.05$), which the authors attributed to a potentially greater ability to tolerate higher doses of NHB.

Other studies have analyzed clinical outcomes in patients without LV recovery to determine the potential morbidity and mortality benefits from NHB in LVAD patients. In the retrospective cohort analysis of INTERMACS, outcomes including survival and quality of life were evaluated in patients who received NHB.[30] Among 12,144 patients who survived 6 months post-LVAD placement, 2,742 (22.6%) received a BB with an ACEi or an ARB; 2,359 (19.4%) received a BB alone; 1,967 (16.2%) received triple therapy with a BB, ACEi or ARB, and MRA; and 1,200 (9.8%) received a BB and MRA. For comparison, 1,725 (14.2%) of the cohort did not receive any NHB. Of note, medications in this group included any combination of the following: digoxin, amiodarone, calcium channel blockers, hydralazine, and phosphodiesterase inhibitors. Compared to patients who did not receive NHB, the triple therapy group had significantly greater survival (68.5%; 95% CI, 65.2%-72% vs. 53.9%; 95% CI, 49.1%-59.4%, $p<0.0001$). When compared to the other medication groups, triple therapy was also associated with significantly greater odds of survival (HR 0.34; 95% CI, 0.28-0.41; $p<0.001$). All combinations of NHB

improved survival with the exception of MRA monotherapy (adjusted HR 0.88; 95% CI, 0.7-1.1, p=0.3). The overall association between NHB and outcome was consistent regardless of LVAD indication. Quality of life estimates via the Kansas City Cardiomyopathy Questionnaire score and 6-minute walk distance also improved when NHB was compared to no NHB. Furthermore, biomarkers including NT-proBNP and average creatinine were each lower in the triple therapy versus no NHB groups. This study represents a large population of patients and provides insight into optimal combinations of NHB with triple therapy. No data are provided on dosing to help guide optimal titration strategies of the medications.

A smaller, single-center retrospective study was conducted in adult patients with HMIIs and either ischemic or dilated cardiomyopathy.[31] Patients were categorized as having received NHB (n=31) versus those who had received no NHB (n=33). Baseline demographics did not vary between groups. Within the NHB group, 20 (64.5%) patients received an ACEi or ARB, 26 (83.9%) received a BB, and 2 (6.5%) received an MRA. Combination therapy groups consisted of 19 (61.3%) patients prescribed an ACEi/ARB plus BB, and 2 (6.5%) patients prescribed ACEi/ARB plus BB plus MRA. NHB was initiated at the discretion of the treating cardiologist to maintain a mean blood pressure below 80 mmHg and a heart rate below 100 beats per minute. On average, patients in the NHB group achieved daily doses of lisinopril (10 mg), enalapril (7.5 mg), or quinapril (15 mg) for ACEi therapy; candesartan (4 mg), telmisartan (40 mg), or losartan (25 mg) for ARB therapy; carvedilol (25 mg), metoprolol (75 mg), and atenolol (50 mg) for BB therapy; and spironolactone (25 mg) for MRA therapy. At 6 months, the percent change in LVEF, LVEDD index, LV index mass, and NT-proBNP was significant in the NHB group (p=0.025, p=0.017, p=0.031, and p=0.011, respectively). These differences were not seen in the no NHB group. Regarding quality of life outcomes, overall New York Heart Association classification was significantly improved in the NHB compared to non-NHB group at 3 and 6 months (p=0.021 and p=0.024, respectively). No numerical data were provided on the change from baseline in any of these parameters. Additionally, in patients who completed the 6-minute walking distance test, those in the NHB group (n=15) experienced a statistically greater improvement than the non-NHB patients (n=13) at 3 months (70.3 ±48.4 m vs. 24.4 ±48.8 m, p=0.019) and 6 months (146 ±58.9 vs. 49.4 ±54.6, p=0.0007) post-implant. The composite outcome of cardiovascular death or hospitalization for HF was significantly less in the NHB group (0% vs. 18.2%, p=0.013). There was no significant difference in all-cause mortality. Although limited by the number of patients included and the non-randomized nature of the patient allocation, this small study indicates improvement in HF parameters, morbidity, and mortality in patients with LVADs prescribed NHB.

Future Directions

Despite the promising role for NHB in patients with LVADs, current evidence is limited by the observational nature of the studies, small sample sizes, and use of different LVAD models. Additionally, many of the studies lack details regarding

medication dose, adherence, and reasons for initiation or discontinuation. However, a synergistic effect between pharmacologic therapy and mechanical unloading leading to improvements in survival, quality of life, and biomarkers was evident. With the majority of data originating from retrospective analyses, prospective trials will need to be conducted in order to corroborate the current body of literature.

There is a gap in the literature on the ideal time to start these medications and the doses that are adequate to achieve morbidity and mortality outcomes. Based on the studies in patients undergoing rigorous protocols for myocardial recovery and LVAD explantation, patients can tolerate early initiation during their index implant hospitalization, as well as moderate to high doses of NHB. The use of sacubitril-valsartan therapy shows promise in reducing MAPs and NT-proBNP without increased harm from adverse effects. Initial outcomes data indicate improved morbidity outcomes with improvements in functional classification.

Conclusions

There is a paucity of data regarding the use of HF therapies in patients with LVADs. In practice, the use of GDMT post-LVAD implant has largely focused on blood pressure management, however, current evidence suggests the use of NHB may increase device explantation rates, increase functional capacity, and decrease mortality. The optimal combination of GDMT appears to be triple therapy with an ACEi or ARB, BB, and MRA. The data suggest MRA use alone does not have an impact on mortality, unlike ACEi or ARB and BB therapy. Thus, HF medications in LVAD patients should first focus on ACEi or ARB and BB initiation prior to MRA therapy. If patients are able to tolerate doses of sacubitril-valsartan without hypotension, hyperkalemia, or serum creatinine increases, it may be reasonable to substitute ARNi therapy for ACEi/ARB in the triple therapy combination described above. As destination therapy becomes a more common indication for device implants and more patients wait for a heart transplant, optimizing these therapies will be critical in the support of patients with LVADs.[32,33]

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